Furthermore, it is fundamentally understood that proteins act and are acted upon through specific binding interactions with other molecules. Identifying molecules that bind to a gene or protein involved in regulating an identified phenotype is a recognized method of identifying additional molecules that can affect regulation of that phenotype. *See, e.g.*, Fields *et al.*, U.S. Patent No. 5,283,173, issued February 1, 1994 (cited by the Office in Paper No. 17).

II. COMBINED REJECTION UNDER 35 U.S.C. §§ 101 AND 112, FIRST PARAGRAPH

A rejection of pending Claims 1, 2, 6, 7, and 48-61 was maintained for an alleged lack of substantial asserted utility or a well-established utility and corresponding lack of enablement under 35 U.S.C. §§ 101 and 112, first paragraph respectively. Applicants traverse the rejection as stated *infra* and for the reasons previously of record. As stated by the Office, the entire basis of the rejection under § 112, first paragraph is dependent on the rejection for lack of utility under § 101.

1. Rejection under 35 U.S.C. § 112, First Paragraph

The Office contends that there are two issues that must be considered separately, as there are two grounds of rejection of the claims under 35 U.S.C. §§ 101 and 112, first paragraph. Applicants disagree.

The Office makes the statement that the question presented in Applicants' Appeal had been ***narrowed to the single issue*** of the credibility of the utility of the claimed invention asserted in the subject Application. Additionally, the rejection under 35 U.S.C. § 112 stands or falls with the rejection under § 101, as no separate lack of enablement rejection was set forth that was not linked with a finding of lack of utility. Examiner's Answer at 6. A separate finding of lack of enablement that is not contingent on a finding of lack of utility is required pursuant to M.P.E.P. § 2107.01 ("IV. Relationship Between 35 U.S.C. 112, First Paragraph, and 35 U.S.C. 101").

Thus, it is clear that the rejection stands or falls on the single issue of the utility of the claimed invention as asserted in the Specification. While Applicants recognize that enablement and utility are separate requirements, the only reason that has been alleged for the rejections under appeal concerns whether the asserted utility is a substantial/well-established and credible utility.

2. **Rejection under 35 U.S.C. § 101**

Turning to the rejection under 35 U.S.C. § 101, it is asserted that the claimed method of identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to, or that inhibits binding of a molecule to, HBM or Zmax1 (Claims 1 and 53) or a method for identifying a candidate molecule involved in lipid regulation (Claim 6), and the related claims that depend there from, lack a substantial and credible utility. The Office acknowledges that "HBM and Zmax1 have specific, credible, and substantial asserted utility in and of themselves because they have been associated with particular lipid profiles." *See, e.g.*, Examiner's Answer at 4. However, the Office alleges that the presently claimed methods nevertheless do not have utility under 35 U.S.C. § 101, and, as a consequence, are not enabled as required under 35 U.S.C. § 112. *See*, Examiner's Answer at 6.

Applicants respectfully maintain that the Office has failed to state a *prima facie* case in support of the rejections, has failed to give proper consideration to the evidence of utility previously presented by Applicants, and has misapplied the standard under which utility is determined. Accordingly, the pending rejections should be withdrawn for the reasons discussed *infra* and of record.

To evince a case of lack of utility, the Office must show that the claimed invention lacks a practical utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); M.P.E.P. 2107.01 ("I. Specific and Substantial Requirements"). To achieve this, the Office must provide evidence sufficient to show that the statement of asserted utility would be considered "***false***" by a person of ordinary skill in the art. The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (*i.e.*, the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false). M.P.E.P. § 2107.02; *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Deficiencies under § 101 occur either in showing that the claimed invention has no apparent use, or in the more rare instance where the invention is not credible. M.P.E.P. § 2107.01.

All that must be shown is that there is a substantial or well established utility and that the claimed utility is credible. A "substantial utility" "defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities." M.P.E.P. § 2107.01 ("Substantial Utility"). The M.P.E.P. goes on to say that screening assays "***have a clear, specific and***

unquestionable utility (e.g., they are useful in analyzing compounds)." *Id.* ("Research Tools"). Applicants claim methods for identifying reagents involved in lipid regulation that bind to or inhibit binding of reagents to HBM or Zmax1. The M.P.E.P. states that "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease conditions would also define a 'real world' context of use in identifying potential candidates for preventative measures or further monitoring." *Id.* Applicants are claiming a method of identifying compounds that modulate lipid interaction by their interaction with Zmax1 or HBM. The Office admits that the genes are associated with a particular lipid profile. As described in Section I above, lipids are involved in, for example, the conditions of atherosclerosis and cardiac disease. Applicants demonstrate in Example 3 of the specification that patients expressing the polymorphic variant, *i.e.* the HBM protein, have a better lipid profile. Namely, their HDL level was higher and their VLDL and triglyceride levels were lower than the control patients' tests. *See* Section I *supra.* Applicants provide an assay method with the real world use of screening reagents for lipid modulation. Thus, the claimed invention has substantial utility.

If the data presented and asserted utility contained in the application is insufficient (which it is not), additional data has since been described clearly demonstrating the link between lipid control and LRP5, where the *Lrp5* gene has been knocked out in mice. This *in vivo* data demonstrated deleterious altered lipid levels as would be expected based on Applicants stated utility. Additionally, in the instance of a combined *Lrp5* knockout, the resulting animals exhibited abnormal triglyceride clearance. *See* discussion of Magoori et al. and Fujino et al. in Section I *supra.*

Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. When an applicant provides data, whether from *in vitro* tests or from animal models or both, to support an asserted utility (which Applicants have done previously as well as now) and an explanation why it supports the utility, the Office will determine if the data is predictive of the asserted utility. M.P.E.P. § 2108.03 (III. Data From *In Vitro* or Animal Testing is Generally Sufficient to Support Therapeutic Utility). Utility is a low hurdle.

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . .

> Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, the defense of non-utility cannot be sustained without proof of total incapacity.

M.P.E.P. § 2107.01 (H. Wholly Inoperative Inventions: "Incredible" Utility).

Applicants submit that the data from the family expressing the HBM variant and the wild-type *Lrp5* gene knock out all demonstrate that the gene and its HBM variant are involved in lipid modulation. The Applicants' (in the Specification) and in the attached publications of Johnson et al. and Little et al. show that a single genetic locus is responsible for the phenotypes measured in this kindred. Furthermore, using a mouse genetic model, Fugino et al. and Magoori et al. have clearly shown that a different variant of Zmax1 (the *Lrp5* null allele), has a dramatic consequence on lipid levels. ***Together these data are more than correlative but rather direct evidence of a cause and effect on lipid levels dependent on the inherited Zmax1 allele.*** Thus, assays and methods for screening compounds that modulate the genes or proteins to identify compounds and compositions that modulate lipids are reasonably correlated to a particular pharmacological utility of identifying reagents that modulate lipid levels for producing new drugs that can regulate lipid-mediated diseases, such as atherosclerosis, is a substantial utility. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient. *Fujikawa v. Wattanasin,* 93 F.3d 1559, 1565, 39 U.S.P.Q.2d 1895, 1900 (Fed. Cir. 1996).

2.1 Addressing the Reference of Ye et al.

The Office has alleged that Ye et al., *Am. J. Clin. Nutr.*, 72: 1275S-1284S, 2000, cast doubt on whether Zmax1 or HBM are involved in lipid regulation. Ye et al. teach that not all lipid affecting polymorphisms respond equally to dietary intervention. Applicants' claimed invention does not relate to diet, which implicates a number of confounding factors not found where one is identifying and using molecules that bind directly to a lipid regulating protein. Ye et al. supports the general proposition that polymorphisms can influence the activity of lipid regulating molecules.

Moreover, Ye et al. teach that genes influence quantitative variations in plasma lipoprotein concentrations. Ye et al. review a series of polymorphisms in various genes involved in lipid regulation. In the section cited on page 6 of the Office Action mailed April 23, 2003, Ye et al. report that studies of the effects of dietary cholesterol have not been

consistent due to a series of confounding factors. This only means that it remains to be determined under what circumstances and for which polymorphisms a dietary intervention is indicated.

More importantly, Ye et al. do not in any way cast doubt on whether those polymorphisms, or the HBM polymorphism, appear in genes related to lipid regulation. Ye et al. only show that diet alone may not have a consistent effect. It certainly does not provide a reason to doubt the utility of the present invention. The question of whether a dietary change can affect lipid profiles simply has no bearing on the question of whether identifying a molecule that binds to a protein involved in lipid regulation (such as HBM or Zmax1) has substantial and credible utility as a method for identifying a molecule that is involved in lipid regulation.

Additionally, the Ye et al. reference does not question the asserted function of LRP5. Nor does the Ye et al. reference provide any other scientific evidence to refute the assertion of lipid regulation in LRP5.[5] The claimed invention does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. Moreover, even if the Office met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, Applicants submit that more than sufficient evidence has been presented to convince one of skill in the art of the asserted utility with the references of at least Magoori et al., Fujino et al., and Little et al. There simply is no evidence to evince the conclusion that Applicants' asserted utility is false.

2.2 Addressing the Reference of Willnow et al.

Willnow et al. (1999 *Nature Cell Biol.* 1: E157-162) also is cited for the position that additional experimentation would be required in order for one of skill in the art to determine if an LDL-receptor family member is actually involved in lipid regulation. Willnow et al. is cited for teaching:

> Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and

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[5] The Court of Appeals for the Federal Circuit argued a similar line of reasoning and somewhat analogous fact pattern in *In re Brana.* The Court stated that "[t]he references cited by the Board, Padur and Martin, do not question the usefulness of any compound as antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests – relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995).

> membrane synthesis. This perception has now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and [*sic*] entirely unexpected new role as transducers of extracellular signals.

Examiner's Answer at 9.

Applicants do not disagree with the basic argument that LDL-receptors can be involved in processes other than lipid regulation. The data of the three Examples in the Specification clearly demonstrate that the Zmax1 variant, HBM, produces a positive phenotype for its host not only in bone mineral density, but also as described in Example 3, for an enhanced lipid profile (*i.e.,* enhanced HDL levels and reduced VLDL levels). The Specification's data coupled with the post-filing data of Magoori et al. and Fujino et al. as discussed in Section I *supra*, clearly demonstrate Zmax1 is involved in lipid regulation. The finding by Applicants lies in congruence with the long observed pattern that bone mineral density and lipid levels (and correspondingly lipid-mediated diseases) are linked. *See* discussion of Parhami et al., *supra.* Willnow et al. fail to teach that LRP5 specifically does not have the effect of modulating lipid levels as indicated by the Specification and as further supported by the data of Little et al., Magoori et al., and Fujino et al. All Willnow et al. asserts is that generally the family of LDL receptors may have more than one function. Certainly, that is true for Zmax1, which is involved in both bone mineral density and lipid modulation.

Applicants do not disagree with the teachings of Willnow et al. However, in view of the data presented in Example 3 of the Specification and the references provided in Section I above, the asserted functions of Zmax1 and HBM are not in doubt. An artisan of ordinary skill would certainly not conclude that the asserted utility is false. The gene and associated encoded protein mediate both bone mineral density and lipid levels. The fact that ***other*** LDL receptor genes mediate ***other*** functions does not alter the observations for Zmax1/HBM as described in the instant specification or as further supported by the references of Little et al., Magoori et al., and Fujino et al. *See also* arguments above for Ye et al.

2.3 Data Disclosed in the Application and the Art of Record

The credibility of the asserted substantial and well-established utility is supported by several lines of direct and circumstantial evidence. In the Examiner's Answer, the Office attacks individual elements of the evidence Applicants have pointed out in the Specification and presented from independent unbiased sources. The Office alleges that each individual piece of evidence is inadequate to establish that Zmax1 or HBM are directly involved in lipid regulation. Examiner's Answer at 13-17. However, it is improper to attack Applicants' evidence as insufficient when each piece is viewed in isolation. Even if, *arguendo*, individual lines of evidence were separately insufficient as alleged, the credibility of the asserted utility is strongly supported by the combination of the evidence ***as a whole***. *See Cross v. Iizuka*, 753 F.2d 1040, 1049, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). The Office is obliged to consider all the evidence of record taken ***as a whole*** from the viewpoint of one of skill in the art. Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098-99 (January 5, 2001); M.P.E.P. § 2107 (Emphasis added).

2.4 Post-Filing Date Evidence

The Office has not seemed to fully consider the post-filing date evidence that were previously submitted. For example, Fujino et al. (2003) and Magoori et al. (2003) have shown that LRP5 is essential for normal cholesterol metabolism. *See* Section I *supra.* Parhami et al. (2001) surveyed the history of links between lipid regulation and bone mineral density citing publications from well before the filing date of the present application (*i.e.*, 1972 and 1992) as demonstrating that osteoporosis and cardiovascular disease are linked regardless of age; the 1972 article of Pinals et al. is attached. *See* Section I *supra.*

In judging the credibility of an asserted utility, the Office is obliged to consider all the evidence that is probative of an applicant's assertions. Utility Examination Guidelines, *supra*; M.P.E.P. § 2107(II)(B)(ii). ***Evidence presented in rebuttal to an allegation that an assertion of utility is not credible must be considered, regardless of publication date.*** *In re Pottier,* 376 F.2d 328, 330 n.1, 153 U.S.P.Q. 407, 408 n.1 (C.C.P.A. 1967) ("[W]hether or not an invention would be deemed operative by one of ordinary skill in the art is determined, not at the time the invention was made but rather (at the earliest) at the time of the examiner's call for proof."); *see also, Gould v. Quigg*, 3 U.S.P.Q.2d 1302, 1304, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

The claimed invention is both useful and enabled as taught in the Specification at the time the application was filed, and as further supported by independent evidence discussed above. Thus, Applicants' asserted utility has practical utility and is credible and true.

For the reasons discussed above and previously of record, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §§ 101 and 112, first paragraph.

CONCLUSION

For at least the foregoing reasons, the Office has failed to state a *prima facie* case in support of the pending rejections under 35 U.S.C. §§ 101 and 112, first paragraph. But, even if the Office did state a *prima facie* case, Applicants have offered more than sufficient evidence to rebut the Office's allegations.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited. In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 02-4800. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for in the papers filed herewith, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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Date: November 22, 2004

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